REMARKS

Claims 24-31 were pending. All pending claims were rejected in the Office Action referenced above. Claims 1-23 and claims 32-49 were canceled. Applicants respectfully request withdrawal of the rejections in view of the following arguments.

In the Notice of Non-Compliant Amendment, it was pointed out that a complete listing of all the claims was not present in the Request for Reconsideration filed February 23, 2004, and that the same was necessary for the amendment to be entered. The instant Supplemental Request for Reconsideration includes a listing of all claims. Entry is earnestly requested. It is asked that the Office use the appendices/attachments forwarded with the Request for Reconsideration filed February 23, 2004.

In the Office Action, the Office maintained the rejection of claims 24-31 under 35 USC 102(e) over Queen et al for, allegedly, the reasons already of record in Paper No. 43. (*See* Office Action, page 2). As will be clear from the discussion below, however, the Office's reasons for rejection have been a moving target.

In the present Office Action, the Office argues that Applicant misquoted the Examiner's position in the Supplemental Response filed March 18, 2003. In the present Office Action, the Office states that

> The Examiner did not state that CDRs means Kabat "plus" Chothia. Rather, the Examiner position is that CDRs, as incorporated by reference by Queen et al in the '975 specification could mean **either** the CDR amino acids defined by Kabat, **or** the amino acids in the hypervariable region taught by Chothia et al (The hypervariable regions are also called CDR's [sic] according to Queen et al, in 07/290975 application, p. 8, last paragraph, bridging p.9).

(*See* present Office Action, sentence bridging pages 3-4, *et. seq.*, emphasis added.) This argument is unavailing for at least two reasons. First, it is contrary to what the Office previously argued or, at a minimum, it is contrary to the argument to which the Office was previously responding. Second, such an interpretation would render the claims indefinite. The latter will be addressed first.

Claim 1 of Queen et al is duplicated below:

> 1. A humanized immunoglobulin having **complementarity determining regions (CDRs)** from a donor immunoglobulin and heavy and light chain variable region frameworks from human acceptor immunoglobulin heavy and light chains, which humanized immunoglobulin specifically binds to an antigen with an affinity constant of at least 10^7 M^{-1} and no greater than about four-fold that of the donor immunoglobulin, wherein said humanized immunoglobulin comprises amino acids from the donor immunoglobulin framework **outside the Kabat and Chothia CDRs**, wherein the donor amino acids replace corresponding amino acids in the acceptor immunoglobulin heavy or light chain frameworks, and each of said donor amino acids:
>
> (I) is adjacent to a CDR in the donor immunoglobulin sequence or
>
> (II) contains an atom within a distance of 4 Å of a CDR in said humanized immunoglobulin.

(*See* Queen et al, claim 1, emphasis added.) The first limitation of claim 1 does not recite "Kabat or Chothia CDRs," but merely "CDRs." The examples in the specification, as acknowledged yet dismissed by the Office as not being germane in the Office Action, define CDRs in terms of Kabat. The general protocol set forth at Column 14 of Queen et al listing the categories of what amino acids may be selected as donor defines CDRs in terms of Kabat (col. 14, lines 1-2). Indeed, the only portion of the file history that is cited to support the Office's "either/or" interpretation is the alleged incorporation by reference of the Kabat and Chothia papers in Application Serial No. 290,975.

Regardless, if, as the Office seems to now be alleging, the first reference merely to CDRs in claim 1 means **either** Kabat **or** Chothia, then claim 1 is clearly indefinite. As acknowledged by Queen et al, the CDRs of Kabat and Chothia are not the same. More specifically, for the heavy chain, the Chothia CDRs are smaller than the Kabat CDRs and are not co-extensive

therewith. For example, the first CDR of the heavy chain per Kabat includes residues **31-35**; for Chothia, the first hypervariable loop includes residues **26-32**. Thus, depending upon which definition is used, a product having changes at residues 26-30, may or may not infringe. Similarly, a product having changes at residues 33-35 may or may not infringe. Further, one cannot tell whether the additional limitation of claim 1 – i.e., "adjacent a CDR in the immunoglobulin sequence" -- is satisfied because the answer will change depending upon the limits of the CDRs.

Second, the Office's present argument seems contrary to its previous arguments and contrived to respond to Applicants' arguments that an interpretation that an interpretation that CDRs includes both is clearly not supported. In the prior Office Action, the Office asserted that

> one of ordinary skill in the art would have recognized that CDR's as taught by Queen et al would **include also** CDR's as defined by Chothia et al, **besides CDR's as defined by Kabat et al**, regardless of whether the rest of the specification discloses as examples Kabat's CDR's.

(*See* Office Action dated as mailed March 26, 2003, page 4, emphasis added.)

Applicants have consistently argued that Queen et al is not entitled to a priority date earlier than the date in which the recitation requiring that the residue(s) to be changed to donor be "outside the Kabat and Chothia CDRs" first appeared because there was no support for this recitation earlier. Indeed, even in the issued Queen et al patent, changes **within** the "Chothia" CDR are clearly viewed as residue changes "**outside** the CDRs." See, for example, the discussion of Category 4 of the protocol for selecting amino acids to change at col. 14, lines 43 *et seq.* of Queen et al and the list of residue changes for the Fd138-80, M195, and mik-β1 antibodies of Table 1, cols. 43-44, of Queen et al. Residues 27, 29, and 30 are all listed as satisfying Category 4 in Table 1. Residues 27, 29,and 30 are all within the "Chothia" CDR, i.e., 26-32. Category 4, however, is defined as follows: "[a] 3-dimensional model, typically of the original donor antibody, shows that certain amino acids **outside** of the CDR's . . . have a good probability of interacting with amino acids in the CDRs by hydrogen bonding." (Queen et al, col. 14, lines 43-47, emphasis added.) Residues 27, 29, and 30 are identified as residues within Category 4 and, thus, are clearly considered to be residues outside the CDRs.

Applicants maintain that there is no written descriptive support in the two earliest filed applications for the requirement that the changes to donor be outside the Kabat **and** Chothia CDRs as recited in the claims as issued in Queen et al. Accordingly, Applicants respectfully submit that the Queen et al is not an appropriate reference under 35 USC 102(e), and this rejection should be withdrawn.

CONCLUSION

Applicants respectfully submit that the application is in condition for allowance and request declaration of an interference. If the Examiner disagrees, or feels a telephonic interview would be helpful, she is asked to contact the undersigned at 215-665-5593 to discuss.

Respectfully submitted,

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